COMMITTEE FOR RISK ASSESSMENT

BACKGROUND DOCUMENT TO THE OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING OF

INDIUM PHOSPHIDE
EC number: 244-959-5
CAS number: 22398-80-7

Final

27 January, 2010

CONTENTS

TABLES

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: Indium phosphide

EC Number: 244-959-5

CAS number: 22398-80-7

Registration number (s): -

Purity: no data

Impurities: no data

Proposed classification based on Directive 67/548/EEC criteria:

Carc. Cat. 2; R45
T; R48/23
Repr. Cat. 3 ; R62

Proposed classification based on CLP criteria:

Carc. 1B – H350
STOT RE 1 – H372 ("Causes damage to lungs through prolonged or repeated inhalation exposure")

Repr. 2 – H361f

Proposed labelling:

R-phrases: R45- 48/23 – 62, Symbol(s) : T, S-phrases : S45- 53 (Directive 67/548/EEC)
GHS08; Dgr; H350, H361f, H372 (CLP)

Proposed specific concentration limits (if any):

Conc. ≥ 0.1%	Carc Cat 2; R45 : T; R48/23
	Carc 1B-H350; STOT RE 1 - H372 ("Causes damage to lungs through prolonged or repeated inhalation exposure")
0.01% ≤ Conc. <0.1%:	Carc Cat 2: R45 : Xn; R48/20
	Carc 1B-H350; STOT RE 2 - H373 ("Causes damage to lungs through prolonged or repeated inhalation exposure")

Proposed notes (if any): Note E

JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name:	Indium phosphide
EC Name:	Indium phosphide
CAS Number:	22398-80-7
IUPAC Name:	Indium phosphide

1.2 Composition of the substance

Chemical Name:	Indium phosphide
EC Number:	244-959-5
CAS Number:	22398-80-7
IUPAC Name:	Indium phosphide
Molecular Formula:	InP
Structural Formula:	Not applicable
Molecular Weight:	145.8 g/mol
Typical concentration (% w/w):	No data
Concentration range (% w/w):	No data

1.3 Physico-chemical properties

REACH ref Annex, §	Property	IUCLID section	Value
VII, 7.1	Physical state at 20°C and 101.3 kPa	3.1	Black brittle crystals with metallic appearance
VII, 7.2	Melting/freezing point	3.2	1062°C
VII, 7.3	Boiling point	3.3	No data
VII, 7.4	Relative density	3.4	4.8 g/cm^3
VII, 7.5	Vapour pressure	3.6	No data
VII, 7.6	Surface tension	3.10	No data
VII, 7.7	Water solubility	3.8	Insoluble in water (no value available). Slightly soluble in mineral acids. Kabe 1996 reported solubility (as indium) between 100 and 200 µg/L in saline.
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7	No data
VII, 7.9	Flash point	3.11	No data
VII, 7.10	Flammability	3.13	Flammable in the form of dust when exposed to heat or flame. Evolves flammable gas (PH3) in contact with water or humid air.
VII, 7.11	Explosive properties	3.14	Explosive reaction with dinitrogen tetraoxide + acetonitrile. Violent reaction with mercury (II) bromide at 350°C.
VII, 7.12	Self-ignition temperature		No data
VII, 7.13	Oxidising properties	3.15	No data
VII, 7.14	Granulometry	3.5	No data
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17	No data
XI, 7.16	Dissociation constant	3.21	No data
XI, 7.17,	Viscosity	3.22	No data
	Auto flammability	3.12	No data
	Reactivity towards container material	3.18	No data
	Thermal stability	3.19	No data
	Other		Can react with moisture or acids to liberate phophine (PH_3); when heated to decomposition, it may emit toxic fumes of PO_x.

Table 1: Summary of physico- chemical properties

2 MANUFACTURE AND USES

2.1 Manufacture

Indium is mostly obtained from zinc alloys, leached with sulphuric acid to obtain pure metal. Indium can combine with phosphorus to produce a semiconducting compound. A polycrystalline ingot is obtained from melting the compounds at high temperature and high pressure. Then, Czochralski method is used to grow single crystals and ingots are cut into wafers.

2.2 Identified uses

Indium phosphide is used as a semiconductor in electronics.

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex I of Directive 67/548/EEC

Currently not classified in Annex I.

3.2 Self classification(s)

No data

4 ENVIRONMENTAL FATE PROPERTIES

Not evaluated in this dossier

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Fischer 344 rats were exposed to particle aerosol of indium phosphide with a mass median aerodynamic diameter (MMAD) of approximately 1.2 µm at 0-1-3-10-30 and 100 mg/m3 for 6h/d, 5d/w for 14 weeks. After 5 days, concentrations can reach 1 mg/g in the lung. The lung clearance half-life was estimated to approximately 200 days. Indium was also detected in blood and serum at concentrations several orders of magnitude less than that observed in lung tissue. Although blood and serum indium concentrations increased with increasing exposure concentration throughout the 14 weeks of exposure, they appeared to be near steady-state throughout the 16-week recovery period (serum concentrations of 0.315±0.021 µg In/g serum at day 96 of exposure and 0.30±0.05 at postexposure day 112 in animals exposed to 30 mg/m3). Indium was detected in the testis at much higher concentrations than in blood or serum, although still several orders of magnitude less than that in the lung. Similarly, testicular indium concentration increased with increasing exposure concentration and throughout the exposure period. Unlike blood and serum indium concentrations, testicular indium continued to increase in all groups following exposure, indicating that indium was accumulating in the testis over time (concentrations of 0.905±0.081 µg In/g testis at day 96 of exposure and 2.15±0.20 at postexposure day 112 in animals exposed to 30 mg/m3) (National Toxicology Program, 2001).

Another NTP study performed in mice and rats for 22 weeks confirms lung as a target for indium accumulation. Deposition and clearance follow a zero-order kinetics, or constant rate. The accumulation of indium is proportional to exposure time and concentration. (National Toxicology Program, 2001)

Absorption:

After intratracheal instillation (size of particle not available), a very small proportion of the dose is absorbed: 0,23% of the dose is recovered in urines, whereas a part is retained in tissues and most of the dose apparently is excreted (via the digestive tract) through mucociliary movements in lungs (Zheng et al., 1994).

Intraperitoneal administration of indium phosphide (purity 99.999%, 75% of particles ≤ 2.4 µm in diameter) mainly results in accumulation in lung and liver (Kabe et al., 1996).

In Syrian golden hamster, InP were administered by intratracheal instillation (purity >99.99%, contains 0.01% zirconium and traces of yttrium, mean count diameter 1.06 µm with geometric standard deviation 1.80). Three mg/kg were given twice a week for 8 weeks. At the end of the exposure period, serum indium concentration were 3.17 µM. Its elimination from serum had a biphasic pattern, with a half-life of 6.2 weeks in the first period and, then, a second half-life of 60 weeks. (Yamazaki et al., 2000)

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

Species	Doses	LD50	Observations and Remarks	Ref.

		(mg/kg)		
Mouse ICR	0, 1000, 3000, or 5000 mg/kg (75% of particles ≤ 2.4 µm in diameter)		There were no signs of toxicity after oral exposure.	(Kabe, et al, 1996)

5.2.2 Acute toxicity: inhalation

No data

5.2.3 Acute toxicity: dermal

No data

5.2.4 Acute toxicity: other routes

Species	Doses	Route	LD50 (mg/kg)	Observations and Remarks	Ref.
Rat Fischer 344	0,1.2 , 6 and 62 µg/kg (1µm diameter particles)	intratracheal instillation	> 62 µg/kg	At highest dose and after 8 days, InP induces desquamation of alveolar epithelial cells and pulmonary inflammation revealed by increase in neutrophils and lymphocytes. LDH, total phospholipid and total cholesterol were also increased in broncho-alveolar lavage fluid.	(Oda, 1997)
Rat Ficher 344	0,1,10 and 100 mg/kg (0.8 µm diameter particles)	intratracheal instillation		Markers of the inflammatory response are increased in broncho-alveolar fluid in a dose-dependant manner: neutrophils number, LDH activity, concentration of total proteins, phospholipids and cholesterol. Lungs are infiltrated by neutrophils and macrophages, eosinophils are exudated and alveolar cells are exfoliated. Macrophages could phagocyte particulates of indium phosphide and explain that they are detected in liver and spleen. These organs are deprived of any histopathological signs.	(Uemura, 1997)

Mouse ICR	0, 1000, 3000, or 5000 mg/kg (75% of particles ≤ 2.4 µm in diameter)	Intra-peritoneally		Intraperitoneal administration caused no mortality but dose-dependent adverse effects in the lung, liver and spleen.	(Kabe, et al, 1996)

5.2.5 Summary and discussion of acute toxicity

No classification is proposed

5.3 Irritation/corrosion

Not evaluated in this dossier

5.4 Sensitisation

Not evaluated in this dossier

5.5 Repeated dose toxicity

5.5.1 Repeated dose toxicity: oral

No data

5.5.2 Repeated dose toxicity: inhalation

Species	Conc. mg/l	Exposure time (h/day)	Duration of treatment	Observations and Remarks	Ref.
Rat Fischer 344/N 20 animals/group	0, 1, 3,10, 30 and 100 mg/m^3 (aerosol) (trace impurities <0.2% including arsenic, selenium, antimony and iron > 0.01%; approxi-	6h/d, 5d/w (week 1 to 4 and 10 to 14) 7d/w (week 5 to 9)	14 weeks	The study was performed according to FDA GLP and was consistent with OECD guideline 413 except that no ophthalmic examination was performed. One male of the high dose group died during the study (no additional details in study report). Final mean body weights and body weight gains of all exposed groups of males (final weight of 93%, 88%, 90%, 89% and 48% of controls respectively at 1, 3, 10, 30 and 100 mg/m^3) and of females of the high dose (final weight of 60% of controls) were significantly less than those of the chamber controls.	(National Tox. Program, 2001)

	mate MMAD: 1.2 µm)			Shallow, rapid, abnormal breathing was observed in males and females exposed to 30 or 100 mg/m3. Animals in the 100 mg/m3 groups exhibited lethargy, thinness, and ruffled fur. After 14 weeks, features of inflammation were observed in all exposed animals: alveolar proteinosis, alveolar cell hyperplasia and inflammatory cells in multiple sites of the lung. Interstitial fibrosis was observed in respectively 0/10, 0/10, 10/10, 10/10, 9/10 and 10/10 males at 0, 1, 3, 10, 30 and 100 mg/m^3 ($p>0.01$ at 3 mg/m3 and higher) and in 0/10, 0/10, 10/10, 10/10, 10/10 and 10/10 females at 0, 1, 3, 10, 30 and 100 mg/m^3 ($p>0.01$ at 3 mg/m3 and higher). Severity generally increased with the dose and mean severity was minimal at 3 mg/m^3, mild at 10 and 30 mg/m^3 and moderate at 100 mg/m^3. The lung of all exposed rats had a gray to black discoloration and lung weights of all exposed groups of males and females were significantly greater ($p<0.01$) than those of the chamber controls and generally increased with increasing exposure concentration. The 2.7- to 4.4-fold increases in the absolute lung weights were attributed primarily to the accumulation of proteinaceous fluid (alveolar proteinosis) within the alveoli. More lymphocytes and mononuclear cells were found in bronchial and mediastinal lymph nodes of exposed animals. Hepatocellular necrosis was revealed by increase in alanine aminotransferase and sorbitol dehydrogenase activities in all males and from 10 mg/m^3 in females. Statistically significant	

				findings of liver necrosis were observed by histopathology at 100 mg/m^3 in males (5/10 animals vs 0 in controls in other treated groups; minimal severity) and females(9/10 animals vs 0 in controls in other treated groups; minimal severity). The incidence of renal nephropathy was significantly increased in 100 mg/m^3 females (1/10, 0/10, 0/10, 1/10, 1/10 and 10/10 females at 0, 1, 3, 10, 30 and 100 mg/m^3). Exposure to indium phosphide affected the circulating erythroid mass in all exposed groups. Haematopoiesis was stimulated at the highest dose in males and females both in bone marrow and in the spleen, consistent with microcytic erythrocytosis. Moderately severe hyperplasia of the bone marrow (males: 0/10, 0/10, 0/10, 0/10, 0/10, 10/10; females: 0/10, 0/10, 0/10, 0/10, 3/10, 10/10) and mild hematopoietic cell proliferation of the spleen (males: 0/10, 0/10, 0/10, 0/10, 0/10, 10/10; females: 0/10, 0/10, 0/10, 0/10, 0/10, 9/10) were significantly increased in males and females exposed to 100 mg/m3.	
B6C3F1 mice 20 animals/group	0,1, 3, 10, 30 and 100 mg/m^3 (aerosol) (material similar to the rat study)	6h/d, 5d/w (week 1 to 4 and 10 to 14) 7d/w (week 5 to 9)	14 weeks	The study was performed according to FDA GLP and was consistent with OECD guideline 413 except that no ophthalmic examination was performed. Mice were more sensitive than rats. At 100 mg/m^3, all animals either died or were removed moribund. At 30 mg/m^3: 1 male and 3 female mice were also removed moribund. Animals in these two groups were lethargic and hardly breathed. Final mean body weights and body weight gains were significantly decreased in males exposed to 3 mg/m^3 and greater (final weight of	(National Toxicology Program, 2001) GLP

				95%, 89%, and 66% of controls respectively at 3, 10 and 30 mg/m^3) and in females exposed to 10 or 30 mg/m^3 (final weight of 89% and 71% of controls, respectively). Males in the 30 mg/m^3 group lost weight during the study. Hematological changes occurred in mice at all doses and were similar to those that occurred in rats. Lungs were discoloured and enlarged. Lung weights of all exposed groups of males and females were significantly greater than those of the chamber controls and generally increased with increasing exposure concentration. The 2.6- to 4.1-fold increases in the absolute lung weights were attributed primarily to the accumulation of proteinaceous fluid (alveolar proteinosis) within the alveoli. Alveolar proteinosis, chronic active inflammation and alveolar epithelial hyperplasia were observed in all exposed animals (p>0.01 at 1 mg/m3 and higher). Inflammation was more severe than in rats. Interstitial fibrosis was observed 0/10, 10/10, 10/10, 10/10, 10/10 and 10/10 males at 0, 1, 3, 10, 30 and 100 mg/m^3 (p>0.01 at 1 mg/m3 and higher) and in 0/10, 10/10, 10/10, 10/10, 9/10 and 10/10 females at 0, 1, 3, 10, 30 and 100 mg/m^3 (p>0.01 at 1 mg/m3 and higher). Severity generally increased with the dose and mean severity was minimal at 1 mg/m^3, mild at 3 mg/m^3, moderate at 10 mg/m^3 and marked at 30 and 100 mg/m^3. Hyperplasia in the bronchial lymph nodes was observed in almost all exposed males and females. In the larynx, squamous metaplasia commonly accompanied by	

				necrosis and suppurative inflammation were observed in some exposed males (0/10, 0/10, 0/10, 9/10, 8/10 and 9/10 at 0, 1, 3, 10, 30 and 100 mg/m^3, $p<0.01$ at 10 mg/m^3 and higher) and females (0/10, 0/10, 0/10, 4/10, 7/10 and 10/10 at 0, 1, 3, 10, 30 and 100 mg/m^3, $p<0.05$ at 10 mg/m^3 and higher). Exposure to indium phosphide induced a microcytic erythrocytosis which was consistent with the observed hematopoietic cell proliferation in the spleen (males: control, 0/10; 1 mg/m3, 5/10; 3 mg/m3, 3/10; 10 mg/m3, 3/9; 30 mg/m3, 6/9; 100 mg/m3, 9/10) (females:1/10, 3/10, 3/10, 0/10, 6/9, 5/10).	
Fischer 344/N rats 60 males and 60 females/group	0-0.03-0.1 and 0.3 mg/ m^3 (aerosol) (trace impurities <0.12% including arsenic, selenium, antimony and iron between 0.01% and 0.02%; approxi-mate MMAD: 1.2 ± 0.1 µm)	6h/d, 5d/w	21 weeks (0.1 and 0.3 mg/ m^3) 105 weeks (0 and 0.03 mg/m^3)	The study was performed according to FDA GLP and was consistent with OECD guideline 453 except that hematology and clinical chemistry were performed at 3 month only and no urinanalysis was performed. At the 3-month interim sacrifice, lung lesions were qualitatively similar but less severe than in the 14-week study. However, because of the severity of the lesions observed after 3 months, treatment also had to be interrupted in rats of 0.1 and 0.3 mg/m^3 groups after 21th week. No death was reported during this period, or later. At the 3-month interim sacrifice, a chronic inflammation was found in rats. Lung weight was increased 1.6 fold to 2.1 fold in groups exposed to 0,1 and 0,3 mg/ m^3. Areas of inflammation were less spread than in the 14-week study and were predominantly subpleural. A significant alveolar hyperplasia considered as regenerative was developed in all	(National Toxicology Program, 2001), (Gottschling et al., 2001)

				males and the low and high-dose groups of females. Indium phosphide particles were found in bronchial and mediastinal lymph nodes. Histochemical analysis of tissues suggests that inflammation could by the consequence of oxidative stress and could lead to cancer. After two years, survival in the 0.03 mg/m^3 group was not affected; abnormal breathing and lethargy were observed after 18 months. Mean body weight changes of exposed males and females were similar to those of the controls. Lesions in the lung similar to those seen at the 3-months interim evaluation were observed in animals evaluated at 5, 7, 9, 11, 12, 13, and 17 months (data not shown). In general, the lesions progressed in the continuously exposed 0.03 mg/m3 group, while the severities of lung lesions remained similar in animals exposed to 0.1 or 0.3 mg/m3 after exposure was discontinued. Additionally, beginning at week 13, lesions similar to those observed at 2 years were observed including one alveolar/bronchiolar adenoma in the 0.3 mg/m3 group at 17 months. At 2 years, nonneoplastic lesions of the lung included atypical hyperplasia, chronic active inflammation, alveolar epithelial metaplasia, foreign body, alveolar proteinosis, and interstitial fibrosis (males: control, 0/50; 0.03 mg/m3, 49/50; 0.1 mg/m3, 50/50; 0.3 mg/m3, 50/50) (females:0/50, 48/50, 50/50, 49/50), and the incidences were significantly increased in all exposed groups. The incidences and severities of alveolar epithelial hyperplasia were increased in 0.1	

				and 0.3 mg/m3 males and females. Alveolar epithelial hyperplasia represented focal lesions located away from the most intense areas of inflammation and was consistent with spontaneous preneoplastic hyperplasia. Additionally, two rare spontaneous lesions, squamous metaplasia and squamous cysts, occurred in exposed groups, and the incidence of squamous cysts was significantly increased in 0.3 mg/m3 females. At 2 years, the incidences of bronchial lymph node hyperplasia were significantly increased in all exposed groups.	
B6C3F1 mice 60 males and 60 females /group	0-0.03-0,. and 0.3 mg/m^3 (aerosol) (material similar to the rat study)	6h/d, 5d/w	21 weeks (0.1 and 0.3 mg/m^3) 105 weeks (0 and 0.03 mg/m^3)	The study was performed according to FDA GLP and was consistent with OECD guideline 453 except that hematology and clinical chemistry were performed at 3 month only and no urinanalysis was performed. 3 months after beginning of exposure, the administration of InP had to be stopped in the 0.1 and 0.3 mg/m^3 groups because of the severity of lung inflammation. The animals are kept until the end of the experiment. At the 3-month interim sacrifice, the incidence of proliferative and inflammatory lesions in the lung was increased in all treated groups. Alveolar epithelium was hyperplasic and marked by proteinosis. Pleural fibrosis was found in most of the animals. Indium phosphide particles were found in lungs and in bronchial and mediastinal lymph nodes. At 2 years, the incidence of inflammation of the heart and the arteries of the heart was elevated in	(National Toxicology Program, 2001)

				treated animals. Survival rates were decreased in all groups at the end of the 2-year period. No correlation between exposure and death could be made because of discontinuity of exposure in two groups. Body weights decreased in the 0.03 and 0.3 mg/m^3 groups in males and in all exposed female groups. Abnormal breathing in all exposed animals was the main observed clinical sign. At 2 years, there were increased incidences of chronic active inflammation, alveolar proteinosis and foreign body (indium phosphide particles) in the lungs of exposed mice. This inflammation was more severe in mice exposed to 0.03 mg/m3 and was least severe in the 0.1mg/m3 group. A prominent feature of the inflammatory process was the presence of pleural fibrosis (diagnosed as lung, serosa, fibrosis) which in many instances appeared to involve both visceral and parietal pleura with adhesions (males: control, 0/50; 0.03 mg/m3, 50/50; 0.1 mg/m3, 49/50; 0.3 mg/m3, 50/50) (females:0/50, 50/50, 47/50, 49/50). The fibrosis was usually focal, but was sometimes expansive and somewhat diffuse. Usually, these fibrotic areas were associated with areas of inflammation. Pulmonary interstitial fibrosis was uncommon. The incidences of pleural mesothelial hyperplasia of the lung were significantly increased in males and females exposed to 0.03 and 0.3 mg/m3(males: control, 0/50; 0.03 mg/m3, 19/50; 0.1 mg/m3, 4/50; 0.3 mg/m3, 6/50) (females:16/50, 3/50, 13/50,	

				49/50). At 2 years, the incidences of hyperplasia and the appearance of foreign bodies in the bronchial and mediastinal lymph nodes were increased in all groups of exposed mice (mediastinal incidence in males: control, 0/50; 0.03 mg/m3, 34/50; 0.1 mg/m3, 17/50; 0.3 mg/m3, 27/50) (mediastinal incidence in females:0/50, 40/50, 11/50, 29/50).	

5.5.3 Repeated dose toxicity: dermal

No data

5.5.4 Other routes: intratracheal instillation

Species	Dose	Treatment	Observations and Remarks	Ref.
Syrian golden hamster 30 animals per group.	2.25 mg/w (purity > 99.99%, mean count diameter 3.2 µm with geometric standard deviation 2.88)	Once per week for 15 weeks Observed up to 105 weeks	Study not performed according to GLP or guideline methods. No effect on body weight or mortality. Body weight gain was slightly affected (significant only over the period of weeks 40 to 42). Indium phosphide particles deposited in lungs around lesions characterized by proteinosis (19/23 exposed; 0/23 controls), alveolar or bronchiolar hyperplasia (9/23 exposed; 0/23 controls); pneumonia (23/23 in the treated group; 7/23 controls), emphysema (11/23 exposed; 0/23 controls), squamous cell metaplasia (1/23 exposed; 0/23 controls) and metaplastic ossification (12/23 exposed; 5/23 controls). The differences observed were judged to be signficant. Particle deposition was also found in lymph nodes in some of the hamsters.	(Tanaka et al., 1996)
Syrian golden hamster	3 mg/kg (purity	Twice per week for 8 weeks	Study not performed according to GLP or guideline methods. Animals were examined after 8, 16, 40, 64	(Yamazaki et al., 2000)

45 males 4 to 8 hamsters sacrificed per sampling time	>99.99%, contains 0.01% zirconium and traces of yttrium, mean count diameter 1.06 µm with geometric standard deviation 1.80)		and 88 weeks. No animal died during the administration period. Three animals died of emaciation during the observation period. Body weights were lower in treated animals compared to controls without any sign of systemic toxicity. The difference in body weight started after the 8-wk exposure period with a maximum difference around wk 48 where body weight in the treated group was approximately 85% of the control group. At the end of the exposure period, serum indium concentration was 3.17 µM. Lung weights were significantly increased at all times; lungs were marked by moderate to severe inflammation during the observation period. Indium particles were found in the bronchio-alveolar space and alveolar septae. Besides these areas, severe sporadical hyperplasia of bronchio-alveolar cells were noticed (severe from week 0 to 64 after last administration and moderate at week 88). Interstitial fibrosis was reported during the observation period and was still severe at week 88 (mild at week 0 after last administration, moderate at week 8 and severe from weeks 16-88). Cell proliferation was assessed by immunostaining of proliferating cell nuclear antigen (PCNA). Expression of PCNA was evident on the nuclei of bronchio-alveolar cells, mostly in the localized hyperplastic lesions and sparsely in the severely inflamed areas. It decreased during the observation period but was still significant after 88 weeks. No mutation in any of the K-ras gene was evident in any of the lesions examined. The authors suggest that the continuous stimulation by accumulated particles could induce hyperplasia but is insufficient to induce neoplasia.	

5.5.5 Summary and discussion of repeated dose toxicity:

The available studies show that repeated inhalation exposure of rats and mice to indium phosphide has the potential to induce severe adverse effects.

In rats, 14-week inhalation exposure up to 100 mg/m^3 indium phosphide did not increase mortality. Mice were more sensitive: all exposed animals at 100 mg/m^3 died or were removed moribund, and at 30 mg/m^3 1/20 males and 3/20 females were removed moribund. These findings show that at least Xn; R48/20 should be applied to indium phosphide, since the increased death rate seen in exposed animals is below the cut off value of 250 mg/m^3 for this classification.

However, the changes seen in the lungs of exposed animals justify a more severe classification. In 14-week studies, alveolar proteinosis, alveolar cell hyperplasia and inflammatory cells in multiple sites of the lung were observed following exposure of male and female animals to indium phosphide aerosol at levels from 1 mg/m^3 (6 h/d). Mice showed greater sensitivity than rats: interstitial fibrosis was evident in mice from 1 mg/m^3 and in rats from 3 mg/m^3. These findings are considered to be signs of serious damage to the lungs.

Furthermore, toxicokinetic data have shown that indium phosphide particles can accumulate in the lungs of rats and mice following inhalation exposure and, in longer term studies, the lung was again seen to be the main target organ. Pleural fibrosis was seen in mice exposed to 0.03 mg/m^3 indium phosphide and above. There was no determination of a no effect level for lung toxicity.

It is therefore proposed to classify this substance with T; R48/23 on the basis of the serious lesions observed in the lungs of both male and female rats and mice. These serious adverse effects were evident following 14-week inhalational exposure to concentrations an order of magnitude below the classification cut-off value of 25 mg/m^3 and were also evident in longer term studies.

According to the CLP Regulation, the cut-off value for specific target organ toxicity (repeated exposure to an aerosol) category 1 based on a 90-day study is 20 mg/m^3. Since indium phosphide clearly can induce lung toxicity below this exposure level, classification STOT Rep. 1 – H372 is therefore also proposed.

Classification according to Directive 67/548/EEC: T; R48/23

Classification according to the CLP Regulation: STOT Rep. 1 – H372

There are several possible constructions for the label H372 for this substance, with the 3 most obvious ones being:

(i) Causes damage to organs through prolonged or repeated exposure; and

(ii) Causes damage to lungs through prolonged or repeated inhalation exposure;

(iii) Causes damage to lungs through prolonged or repeated exposure.

The first of these is technically accurate, but fails to warn of the specific hazard to the lungs. RAC would prefer not to apply this phrase.

The second is also technically accurate, but fails to cover the possibility of hazards in other tissues or via other exposure routes. It is questionable whether the effects of indium phosphide seen on the rat liver could justify classification and merit a specific warning on the label. In the 14-week rat study, histopathological observations indicated liver necrosis of minimal severity at 100 mg/m^3. However, in the comparable mouse study, no significant liver toxicity was seen. Overall, it is judged by RAC that this doesn't merit classification or a specific warning on the label.

The third label, like the second, draws attention only to the lungs, but it seems inappropriate because it doesn't specifically also mention inhalation exposure as being the concern. The labelling criteria indicate that it should be clear no other routes of exposure can cause the hazard of concern before opting to specify just one or two routes on the label. Although no helpful information regarding repeated oral or dermal exposure to indium phosphide is available, an assessment can be made on the basis of the acute toxicity data. After oral dosing of mice with up to 5000 mg/kg indium phosphide, Kabe et al (1996) found no evidence of toxicity. In contrast, dosing of comparable doses by the non-physiological intra-peritoneal route did produce toxicity to the lungs, liver and spleen. This provides reassurance that the oral route is not a concern. . There are no dermal studies, but considering the predicted very low dermal absorption, no significant toxicity is expected after dermal exposure. In view of this, RAC concluded that it would be appropriate to warn specifically on the label of the danger of inhalational exposure, which after all is the basis for justifying the harmonisation of this endpoint.

Therefore, based on lack of acute oral toxicity, the expected very low dermal absorption, and by applying expert judgement, it is proposed that label H372 for indium phosphide should be option (ii) above, warning specifically of the danger posed to the lungs by inhalation exposure of indium phosphide.

Label H372:

Causes damage to lungs through prolonged or repeated inhalation exposure

Specific concentration limits for repeated dose toxicity

A specific concentration limit (SCL) can be calculated for repeated dose toxicity. The calculation of a SCL for repeated dose toxicity is based on comparing the effective dose (ED) in a study of a specified length, with a guidance value (GV) for the corresponding length of study (SCLCat.1 = ED/GV x 100 %). GVs are presently defined in the CLP guidance for 28 and 90 days studies. It is, however, not evident if toxicity data on indium phosphide from the 90 days study or the 2 years study should be used.

Thus, a SCL can be calculated based on comparing the effective dose (ED) of 0.001 mg/l (1 mg/m3) in mice exposed to indium phosphide for 90 days with the guidance value (GV) of 0.02 mg/l for 90 days studies. At the dose of 0.001 mg/l, minimal interstitial fibrosis was observed in all exposed animals, but no NOAEL was observed. On the basis of these data, the SCL would become 5%. However, the ED used here is a LOAEL, and it is not known if the use of lower doses in that study could have led to an even lower LOAEL. Consequently, this SCL is not viewed by RAC with confidence, especially in the light of the much lower LOAEL observed in the 2 years study.

Pleural fibrosis was reported in the 2 year mouse study, including at the 3 months interim sacrifice. It is therefore also possible to make a calculation for a specific concentration limit based on this study. The SCL can be calculated based on a 90 days ED of 0.03 mg/m^3 (from the 2 years study, equivalent to 0.00003 mg/litre) and the GV for 90 days studies. Thus, the SCL will be calculated as follows; (0.00003 mg/litre) / (0.02) x 100% = 0.15%. The SCL should according to the guidance be rounded of, and a final SCL of 0.1% is set for repeated dose toxicity.

A SCL of 0.1% is proposed for repeated dose toxicity (T;R48/23, STOT1), and 0.01% for Xn; R48/20 (STOT2).

5.6 Mutagenicity

5.6.1 In vitro data

No data are available.

5.6.2 In vivo data

Somatic cells

Test	Species	Exposure route & Harvest time	Observations and remarks	Ref
Micronucleus test in peripheral blood	B6C3F1 mice	Inhalation 14-week (aerosol similar to repeated exposure toxicity study)	The study was consistent with OECD guideline 474 except that no positive control results were reported. No significant genetic damage is highlighted by the test.	(National Toxicology Program, 2001)

No data in germ cells are available.

5.6.3 Human data

No data

5.6.4 Summary and discussion of mutagenicity

→ No classification required.

5.7 Carcinogenicity

5.7.1 Carcinogenicity: oral

No data

5.7.2 Carcinogenicity: inhalation and intra-tracheal instillation

Species	Conc. mg/l	Exposure time (h/day)	Observations and Remarks	Ref
B6C3F1 mice 50 animals/ group	Inhalation 0, 0.03, 0.1 and 0.3 mg/m^3	0.03 mg/m^3 for 2 years, 0.1 and	Performed according to FDA GLP and was consistent with OECD guideline 453 except that hematology and clinical chemistry were performed at 3 month only and no urinanalysis was performed.	(National Toxicology Program, 2001)

	(aerosol) (trace impurities<0.12% including arsenic, selenium, antimony and iron between 0.01% and 0.02%; approximate MMAD: 1.2 ± 0.1 µm)	0.3 mg/m^3 for 21 weeks, with sacrifice at 2 years	Besides inflammation of the lung, adenomas and carcinomas were noticed in mice exposed to indium phosphide. It has to be noted that no dose-effect correlation can be made since exposure of the groups 0.03 and 0.1 mg/m^3 were interrupted after 21 weeks. A clear increase in carcinoma of alveolar and bronchiolar cells was seen in lungs. The overall rates of alveolar/bronchiolar carcinoma were 6/50 (12%), 15/50 (30%), 22/50 (44%) and 13/50 (26%) in males treated with 0, 0.03, 0.1 and 0.3 mg/m^3, respectively and 1/50 (2%), 6/50 (12%), 5/50 (10%) and 7/50 (14%) in females. The corresponding survival-adjusted rates were respectively 12.9%, 36.5%, 48.6% and 29.7% in males and 2.1%, 15.8%, 10.8% and 17.6% in females. The rates were significant at all doses in males and at the low and high doses in females. Historical incidences for NTP 2-year feeding studies were 23/249 (mean 9.2%±3.9% - range 4%-14%) in males and 3/250 (mean 1.2%±1.1% - range 0%-2%) in females. Some of these tumours were characterised by a great anaplasia, often spread from the lung into the mediastinum and distant metastases. Mice also developed hepatocellular adenoma and carcinoma. Hepatocellular carcinoma: 11/50 (22%), 22/50 (44%), 23/50 (46%) and 16/50 (32%) in males treated with 0, 0.03, 0.1 and 0.3 mg/m^3, respectively; and 6/50 (12%), 17/50 (34%), 8/50 (16%) and 10/50 (20%) in females. The corresponding survival-adjusted rates were respectively 23.2%, 46.4%, 47.3% and 36.1% in males and 12.7%, 41.7%, 17.4% and 24.7% in females. The rates were significant at the low and medium doses in males and at the low dose in females. Historical incidences for NTP 2-	

			year feeding studies were 50/299 (mean 20.1%±4.2% - range 16%-27%) in males and 52/249 (mean 20.9%±9.1% - range 12%-36%) in females. A non significant increase in rare neoplasms in the small intestine was noticed in males: there is one adenoma or carcinoma in controls versus 2 to 6 in treated groups.	
F344/N rats 50 animals/group	<u>Inhalation</u> 0, 0.03, 0.1 and 0.3 mg/m^3 (aerosol) (material similar to the mice study)	0.03 mg/m^3 for 2 years, 0.1 and 0.3 mg/m^3 for 21 weeks, with sacrifice at 2 years	Performed according to FDA GLP and was consistent with OECD guideline 453 except that hematology and clinical chemistry were performed at 3 month only and no urinanalysis was performed. In rats, adenoma or carcinoma of alveolar and bronchiolar cells was increased in lungs. Alveolar/bronchiolar carcinoma: 1/50 (2%), 10/50 (20%), 8/50 (16%) and 16/50 (32%) in males treated with 0, 0.03, 0.1 and 0.3 mg/m^3, respectively and 1/50 (2%), 3/50 (6%), 1/50 (2%) and 11/50 (22%) in females. The rates were significant at all doses in males and at the high dose in females. The survival-adjusted rates of alveolar/bronchiolar adenomas and carcinomas was provided and were respectively 17.1%, 48.7%, 69.8% and 76.1% in males and 2.3%, 23.5%, 13.5% and 58.8% in females. The rates were significant at all doses in males and at the low and high doses in females. Historical incidences for NTP 2-year feeding studies were 14/299 (mean 4.7%±4.8% - range 0%-14%) in males and 5/299 (mean 1.7%±2.3% - range 0%-6%) in females. In males, 4 animals with squamous cell carcinoma were seen at the high dose whereas none were found in controls and at the low and medium doses. Historical incidence for NTP 2-year feeding studies was 0/299 in males. Pheochromocytoma development from adrenal medulla was also observed: 0/50 (0%), 3/50 (6%), 3/50 (6%) and 1/50 (2%)	(National Toxicology Program, 2001)

			in males treated with 0, 0.03, 0.1 and 0.3 mg/m^3, respectively and 0/50, 0/50, 0/50 and 1/50 (2%) in females. The rates were not significant. The historical incidence for NTP 2-year feeding studies was 5/299 (mean 1.7%±1.5% - range 0%-4%) in males (not given in females). The survival-adjusted rates of benign and malignant pheochromocytoma were 23.8%, 57.1%, 42.6% and 53.1% in males, and 4.6%, 14.5%, 4.5% and 20.6% in females. The rates were statistically significant in males at the low and high doses and at the high dose in females. Historical incidences for NTP 2-year feeding studies were 35/299 (mean 11.7%±5.0% - range 6%-20%) in males and 14/299 (mean 4.7%±2.1% - range 2%-8%) in females. The following uncertain neoplasms were described: skin fibroma (1/4/7/3) and mononuclear cell leukaemia (16/23/29/25) in males and mammary gland carcinoma (0/8/3/2), and mononuclear cell leukaemia (04/21/14/24) in females.	

5.7.3 Carcinogenicity: dermal

No data

5.7.4 Carcinogenicity: human data

In two studies reporting cancer incidence in workers of semiconductors industry, indium phosphide is one of the possible carcinogens (Table 2).

The first study was conducted in the West Midlands in England. In this cohort of 1807 workers, melanoma and non-melanoma skin cancer incidences were increased (2 and 1.5-fold). (Sorahan et al., 1992). The cohort was updated in 2005 and the excess risk of skin melanoma was still significant and an excess risk of rectal cancer was identified (Nichols et al., 2005).

In the second study perform in Scotland in a 4388 workers cohort, an excess (3.9 fold) of lung cancers was found in females; a small excess of stomach cancer in women was also noticed. (McElvenny et al., 2003).

Table 2 – Summary of main results in the cancer cohort studies

Cohort description	Estimation of exposure	Cancer site	Risk	Observations and remarks
(Sorahan, 1992) N=1807 workers (1526 women) first employed in or before 1970 at a semiconductor factory, followed up until 1989 for mortality and 1988 for cancer incidence	Information on dates of hire and leaving employment only. Full work histories not known. A wide variety of chemicals was in use at the plant but worker exposure to these chemicals is believed to have been well controlled.	All All Respiratory Skin-melanoma Skin – non-melanoma	SMR=0.72 (95% CI: 0.59-0.87) SRR=0.96 (95% CI: 0.77-1.18) SRR=0.97 (95% CI: 0.48-1.74) SRR=2.00 (95% CI: 0.41-5.84) SRR=1.52 (95% CI: 0.81-2.59)	SMR and SRR were adjusted for socio-economic status. A total of 3 cases of melanoma were reported.
(Nichols, 2005) N=1807 workers (1526 women) first employed in or before 1970 at a semiconductor factory, followed up until 2002 for mortality and 2001 for cancer incidence Reference: general population of England and Wales	Information on dates of hire and leaving employment only. Full work histories not known. A wide variety of chemicals was in use at the plant but worker exposure to these chemicals is believed to have been well controlled.	All neoplasms All malign. neoplasms Respiratory Skin-melanoma Skin – non-melanoma Rectum	SMR=0.77 (95% CI: 0.63-0.92) SRR=1.00 (95% CI: 0.87-1.13) SRR=0.81 (95% CI: 0.53-1.20) SRR=2.17* (95% CI: 1.12-3.79) SRR=1.10 (95% CI: 0.77-1.53) SRR=1.99* (95% CI: 1.20-3.79) *p<0.05	SMR and SRR were adjusted for socio-economic status. A total of 12 cases of melanoma and 19 cases of rectum cancer were reported.

(McElvenny, 2003) N=4388 workers (2262 women) employed at a Scottish semiconductor manufacturing facility on or before 30 April 1999, followed up until 2000 for mortality and 1998 for cancer incidence (mean length of follow-up: 12.5 years) Reference: Scottish rates	The only exposure indicator was an identification of individuals who worked in the fabrication areas (51% of males and 79% of females). The following known or suspected carcinogens were also present in the factory: antimony trioxide, arsenical compounds, arsine, asbestos in building, chromium trioxide, kaewool, highly refined mineral oil, sulphuric acid mists, ionizing radiation, UV radiation, krypton 85, cabon tetrachloride, chromic acid, trichloroethane, trichloroethylene	All malignant neoplasms (females) Respiratory (females) Stomach (female) Breast (females) All malignant neoplasms (males) Respiratory (males) Stomach (males)	SMR=110 (95% CI: 69-164) SRR=111 (95% CI: 83-145) SRR=245* (95% CI:122-438) SRR=438 (95% CI:90-1281) SRR=134(95% CI:82-206) SMR=47 (95% CI:17-102) SRR=99 (95% CI: 64-147) SRR=71 (95% CI:15-207) SRR=0 (95% CI:0-441) *p<0.05	SMR and SRR were adjusted based on the Carstairs index of deprivation, which take into account average health profile of the economically deprived areas of Scotland. Female stomach cancer (3 cases observed): all cases were in women aged <50 years and with a latency between 5-10 years. Female lung cancer (11 cases): excess was higher in those cases with <10 years latency than for latency > 10 years. Cases had a relatively high age at hire and therefore potential exposures prior employment at the facility. Female breast cancer (20 cases): adjustment with reproductive history was not performed.

5.7.5 Summary and discussion of carcinogenicity

→Two epidemiological studies of cohorts in the semiconductor industry are available. Nichols and Sorahan (2005) reported an excess of risk of melanoma and rectum cancer; McElvenny et al (2003) reported a significant excess of lung cancer in women, and non-significant excess of stomach and breast cancer in women. Due to the limited size of each cohort, the limited information on exposure history and the potential for exposure to other hazardous agents, and the lack of consistency of results between the two cohorts, it has not been possible to draw a conclusion on the carcinogenic effect of indium phosphide in humans. Consequently, a classification in category 1 for carcinogenicity would not be justified.

Two animal carcinogenicity studies involving long-term inhalation exposure to indium phosphide are available. These have shown an increased incidence of lung tumours following repeated exposure of male and female rats and mice to 0.03, 0.1 and 0.3 mg/m^3 indium phosphide.

There are limited data available to fully elucidate the mode of action of indium phosphide in these animals, but the lungs are clearly a key target organ for the toxicity of this substance and the findings are judged to be of relevance to humans. The role of oxidative stress in the lung pathogenesis was studied by assessing the expression of four different markers in different cell types of paraffin-embedded lungs from the rat carcinogenicity study (NTP, 2001; Gottschling et al (2001). The markers were inducible nitric oxide synthase (i-NOS), cyclooxygenase 2 (COX-2), glutathione S-transferase Pi (GST-Pi), and 8-hydroxydeoxyguanosine (8-OHdG). The expression of these markers was in general increased in inflammatory, hyperplastic, and neoplastic cells, both in controls and exposed animals. The expression appeared higher in exposed animals, but it is difficult to interpret the data. The authors interpreted the data as supporting the hypothesis that indium phosphide causes oxidative stress that leads to inflammation (as seen by histopathology), and subsequently to pulmonary cancer.

Given the evidence for carcinogenicity in two species, following inhalation, it is proposed that indium phosphide should be classified as a category 2 carcinogen.

For information, all the data reviewed by IARC (IARC, 2006) in their review of the carcinogencity of indium phosphide has been taken into account in this assessment.

Additional supporting evidence is available, most notably the relatively high incidence of malignant tumours in the livers of mice exposed to indium phosphide by inhalation. It is, however, noted that B6C3F1 mice are known to be very sensitive to liver tumour formation, with a high background incidence, and that liver tumours in this mouse strain generally are considered to have little relevance for humans.

There is insufficient evidence to conclude that indium phosphide would only be carcinogenic following inhalation exposure, therefore labelling phrase R45 is judged to be more appropriate than R49.

The equivalent classification according to the CLP regulation is category 1B. Labelling phrase H350 (with no route of exposure specified) is similarly justified.

Classification according to Directive 67/548/EEC: Carc Cat 2; R45

Classification according to the CLP Regulation: Category 1B; H350

Based on the relatively low exposure concentrations of indium phosphide found to induce lung tumours in rats and mice, a case can be made for the setting of a specific concentration limit for carcinogenicity.

According to the "Guidelines for setting specific concentration limits for carcinogens in Annex I of Directive 67/548/EEC", a lower concentration limit may be set for carcinogens exhibiting high potency. This may be assessed using the "T25" method or, when appropriate, by consideration of other potency factors.

Indium phosphide is carcinogenic to the lungs of rats and mice, males and females. Increased tumours were seen at 0.1 mg/m^3 and 0.3 mg/m^3 at 2 years when the animals had only been exposed for 21 weeks. After 2 years, increased lung tumours were seen at 0.03 mg/m^3 indium phosphide. The overall survival-adjusted rates of alveolar/bronchiolar adenoma and carcinoma in groups of exposed animals ranged from 10-49% in mice and 13-76% in rats. The high frequency tumour formation at low exposure concentrations and short exposure periods clearly indicate a rather "high potency".

Melnick et al (2003) have compared carcinogenic effects of inhaled, non-fibrous, poorly soluble particulates, and found indium phosphide to be the most potent of the 7 studied substances. This analysis of the comparative profiles for similar lung carcinogens supports a "high potency".

The T25 method provides an estimate of potency that is defined as the daily dose (in mg/kg bodyweight) inducing a tumour incidence of 25% over a lifetime exposure. The denominator of mg/kg bodyweight is relevant for chemicals that cause cancer as a result of entering the body and being circulated systemically - this is because the body burden value in "mg bw" is for the whole body, not a site of initial contact on the periphery. However, for a carcinogen acting predominantly towards the lung, following inhalation exposure, and possibly therefore could be defined a non-systemic contact carcinogen, it is not clear to what extent the T25 method applies. However, indium phoshpide is systemically available, even though the availability may be rather low. Considering the proposed mode of action (ROS-formation) and the systemic bioavailability, carcinogenicity by other exposure routes can't be ruled out, and indium phosphide should not be considered a site of contact carcinogen. The T25 method can according to the guidance be used for respirable particles, and it therefore seems relevant to perform calculations for the lung tumours according to the T25 method.

The "model" applied to calculate T25 assumes that dose-response is evident. However, in the available carcinogenicity studies on indium phosphide, there was a high toxicity in the chronic studies that resulted in exposure being stopped by the laboratory after 21 weeks in the mid and high dose groups. Consequently, although a clear dose-response was not seen in this study, this is considered to have been linked to the study design rather than a true reflection of the dose-response profile. With this potential limitation noted, the use of the T25 approach is still considered justified. It should also be noted that the low dose in some cases caused an approximately 25% tumour incidence.

The estimation of T25 will be based on animal studies, in particular the rat and mice NTP inhalation studies, which are considered as robust studies. A linear dose response relationship between and above the experimental doses is assumed. The point of departure for calculation of T25 is the

incidence of a malignant tumour at the lowest dose inducing a significant increase in this tumour[1]. Calculation is made for each study, each sex and each tumour type separately and the lowest estimated T25 is retained:

- **Male mice**

Lowest dose with a significant increase in malignant tumour incidence:
Alveolar/bronchiolar carcinomas (survival-adjusted rate):
Control: 12.9%
0.03 mg/m^3 : 36.5%
Net %: 23.6%
Daily dose in mg/kg bw during a chronic exposure period (based on default values):_
Daily dose: 0.03 µg/L x 1.8 L/h x 6 h/d = 0.324 µg/d
Daily dose per mg/kg bw: 0.324/0.030 = 10.8 µg/kg bw/d
Correction for 5 d/wk dosing: 10.8 x5/7 = 7.71 µg/kg bw/d
T25 based on alveolar/bronchiolar carcinomas in male mice:
T25= 25/23.6 x 7.71 = 8.7 µg/kg bw/d

- **Female mice**

Lowest dose with a significant increase in malignant tumour incidence:
Alveolar/bronchiolar carcinomas (survival-adjusted rate):
Control: 2.1%
0.03 mg/m^3 : 15.8%
Net %: 13.7%
Daily dose in mg/kg bw during a chronic exposure period (based on default values):_
Daily dose: 0.03 µg/L x 1.8 L/h x 6 h/d = 0.324 µg/d
Daily dose per mg/kg bw: 0.324/0.025 = 13.0 µg/kg bw/d
Correction for 5 d/wk dosing: 13.0 x 5/7 = 9.26 µg/kg bw/d
T25 based on Alveolar/bronchiolar carcinomas in female mice:
T25= 25/13.7 x 9.26 = 16.9 µg/kg bw/d

- **Male rats**

Lowest dose with a significant increase in malignant tumour incidence:
Alveolar/bronchiolar carcinomas :
Control: 1/50 (2%)
0.03 mg/m^3 : 10/50 (20%)
Net %: 18%
Daily dose in mg/kg bw during a chronic exposure period (based on default values):_
Daily dose: 0.03 µg/L x 6.0 L/h x 6 h/d = 1.08 µg/d
Daily dose per mg/kg bw: 1.08/0.50 = 2.16 µg/kg bw/d
Correction for 5 d/wk dosing: 2.16 x 5/7 = 1.54 µg/kg bw/d
T25 based on alveolar/bronchiolar carcinomas in male rats:
T25= 25/18 x 1.54 = 2.1 µg/kg bw/d

- **Female rats**

Lowest dose with a significant increase in malignant tumour incidence:

[1] Rapporteur's comment: the T25 calculations were provided by the French authority that submitted the original proposal. It was not indicated why survival-adjusted rates were used for the mouse data, but not for the rat data, but this did not have an impact on the weight of evidence assessment made by RAC.

Alveolar/bronchiolar carcinomas :
Control: 1/50 (2%)
0.03 mg/m^3 : 3/50 (6%)
Net %: 4%
Daily dose in mg/kg bw during a chronic exposure period (based on default values):_
Daily dose: 0.03 µg/L x 6.0 L/h x 6 h/d = 1.08 µg/d
Daily dose per mg/kg bw: 1.08/0.35 = 3.09 µg/kg bw/d
Correction for 5 d/wk dosing: 3.09 x 5/7 = 2.2 µg/kg bw/d
T25 based on alveolar/bronchiolar carcinomas in male rats:
T25= 25/4 x 2.2 = 13.8 µg/kg bw/d

The T25 values for alveolar/bronchiolar carcinomas is in the range of 2-17 µg/kg bw/day for both sexes in both rats and mice, values well below the cut off value (1 mg/kg/day) defined in the SCL guidance for high potency carcinogens.

Therefore, on the basis of a weight of evidence analysis based on;

- T25 values for lung tumours in rats and mice qualifying indium phosphide as a high potency carcinogen,
- a comparison with similar lung carcinogens showing indium phosphide to be the most potent one, and
- very short exposure periods needed for carcinogenicity,

indium phosphide is defined a carcinogen of high potency and a Specific Concentration Limit (SCL) of 0.01% is set.

5.8 Toxicity for reproduction

5.8.1 Effects on fertility

No reproductive study has been performed on indium phosphide but some repeated-dose studies report data on reproductive organs and function.

5.8.1.1 Inhalation

Species	Conc. mg/l	Exposure time (h/day)	Duration of treatment	Observations and Remarks	Ref.
Rat Fischer 344/N 20 animals/group	0, 1, 3,10, 30 and 100 mg/m^3 (aerosol) (trace impurities <0.2% including	6h/d, 5d/w (week 1 to 4 and 10 to 14) 7d/w (week 5 to 9)	14 weeks	The study was performed according to FDA GLP and was consistent with OECD guideline 413 except that no ophthalmic examination was performed. General toxic effects are described in section 5.5.2. In females, no effect was seen on estrous cycle parameters. Ovarian	(National Toxicology Program, 2001)

	arsenic, selenium, antimony and iron > 0.01%; approxi-mate MMAD: 1.2 µm)			atrophy (small with small follicles and corpora lutea and condensed stroma) and uterine atrophy (decreased uterine horn diameter, stromal condensation, shrunken glands) was reported in all females at 100 mg/m^3. In males, degenerating cells from testicular germinal epithelium were present within seminiferous tubules in 5/10 males and within epididymis in all males of the 100 mg/m3 group and were considered secondary to debilitation. Cauda epididymis weight was significantly decreased at 30 mg/m3 with a weight of 90% of controls. In this group the body weight was 89% of controls. No significant differences were noted in sperm morphology. Reproductive tissue evaluation (male reproductive organ weight and sperm count and motility) and estrous cycle characterization were not performed at 100 mg/m3.	
B6C3F1 mice 20 animals/group	0,1, 3, 10, 30 and 100 mg/m^3 (aerosol) (material similar to the rat study)	6h/d, 5d/w (week 1 to 4 and 10 to 14) 7d/w (week 5 to 9)	14 weeks	The study was performed according to FDA GLP and was consistent with OECD guideline 413 except that no ophthalmic examination was performed . General toxic effects are described in section 5.5.2. Uterine atrophy (decreased uterine horn diameter, stromal condensation, shrunken glands) was observed in 4/10 and 8/10 females administered with 30 and 100 mg/m^3, respectively and ovary atrophy (without or with poorly developed corpora lutea) in 9/10 females administered with 30 and 100 mg/m^3. These lesions occurred mainly in animals that died before the end of the study and were	(National Toxicology Program, 2001)

				considered secondary effects. Estrous cycles were longer than 5 five days or unclear in 5/8 animals at 30 mg/m3 and in 1/10 animals in controls. In males, testis weight was significantly decreased at 10 and 30 mg/m^3 with a weight of respectively 93 and 91% of control testis weight. In these groups the body weights were respectively 87 and 64% of controls. Cauda epididymis (73% of controls) and epididymis (81% of controls) weights were also significantly decreased at 30 mg/m^3. No significant differences were noted in sperm morphology. Reproductive tissue evaluation (male reproductive organ weight and sperm count and motility) and estrous cycle characterization were not performed at 100 mg/m^3.	
Fischer 344/N rats 60 males and 60 females/group	0-0.03-0.1 and 0.3 mg/ m^3 (aerosol) (trace impurities <0.12% including arsenic, selenium, antimony and iron between 0.01% and 0.02%; approxi-mate MMAD: 1.2 ± 0.1 µm)	6h/d, 5d/w	21 weeks (0.1 and 0.3 mg/ m^3) 105 weeks (0 and 0.03 mg/m^3)	The study was performed according to FDA GLP and was consistent with OECD guideline 453 except that hematology and clinical chemistry were performed at 3 month only and no urinanalysis was performed. General toxic effects are described in section 5.5.2. No significant histopathological findings were observed in the genital system of males and females. Reproductive tissue evaluation and estrous cycle characterization were not performed.	(National Toxicology Program, 2001), (Gottschling et al., 2001)

B6C3F1 mice 60 males and 60 females /group	0-0.03-0.1 and 0.3 mg/m^3 (aerosol) (material similar to the rat study)	6h/d, 5d/w	21 weeks (0.1 and 0.3 mg/ m^3) 105 weeks (0 and 0.03 mg/m^3)	The study was performed according to FDA GLP and was consistent with OECD guideline 453 except that hematology and clinical chemistry were performed at 3 month only and no urinanalysis was performed. General toxic effects are described in section 5.5.2. No significant histopathological findings were observed in the genital system of males and females. Reproductive tissue evaluation and estrous cycle characterization were not performed.	(National Toxicology Program, 2001)

5.8.1.2 Intratracheal instillation

Species	Route	Dose	Exposure time (h/day)	Observations and Remarks	Ref.
Syrian golden hamster 45 males 4 to 8 hamster per sampling time	Intra-tracheal instillation (purity >99.99%, contains 0.01% zirconium and traces of yttrium, mean count diameter 1.06 µm with geometric standard deviation 1.80)	3 mg/kg	Twice/w for 8 w	Study not performed according to GLP or guideline methods. 8-week exposure followed by 88-week observation period, during which animals were periodically sacrificed. Body weight in the treated group was similar to control group immediately after the last instillation. A decrease was significant from weeks 16 to 64 after instillation and body weight was 80-90% of controls during this period. Body weight became compatible with the control value again 88 weeks after the last instillation. The results of this study concerning the pulmonary toxicity have been reported in Yamazaki 2000 (see section 5.5.4) Weights of testes and epididymis decreased after the exposure period, representing 60-70 % of the control values between the 16th and the 64th	(Omura et al., 2000)

				week. Values reached control levels during the week 88. Caudal sperm count decreased significantly immediately after exposure, and further decreased to 40-50% of control values from weeks 16 to 64 after the last instillation. Values normalised after 88 weeks. From weeks 16 to 88 after instillation, 30-50% of seminiferous tubules have histopathologic alterations, whereas expected abnormalities linked to age are observed in 14% of seminiferous tubules in controls at week 88. The increase is statistically significant compared to controls at weeks 16 and 64. Percentage in the treated group would be lower (14.2%) at 88th week if one particularly affected animal was not included. Histologic alterations included degeneration and loss of germ cells, exfoliation and disarrangement of seminiferous epithelium and atrophy of seminiferous tubules but without alteration of spermatogonia.	

5.8.2 Developmental toxicity

Not evaluated in this dossier.

5.8.3 Human data

No data

5.8.4 Summary and discussion of fertility

Effects on male genital organs (absolute and relative weight loss of testes and epididymes, decrease in sperm count and histopathological lesions in seminiferous tubules) were observed in hamsters in one study after intra-tracheal instillation of 3mg/kg indium phosphide twice a week for 8 weeks.

Interpretation of the study is however limited by the single dose level used and the absence of direct assessment of fertility function. Also, the study is reported in 2 papers available in the open literature: Yamazaki et al 2000, and Omura et al 2000. It is clear from the data that body weight gain is slightly reduced by the exposure to indium phoshide, leading to lower body weights of the exposed animals during the study. The two papers are not very thorough, and when it comes to effects on body weights not internally consistent. At the end of the exposure period the difference in body weight is statistically significant according to Yamazaki et al (2000), by some 6% as estimated

from figure 1A of that report, whereas no difference was seen in body weights according to Omura et al (2000). Furthermore, Yamazaki reports a maximally 6% lower body weight at week 16 post-exposure, whereas figure 1B of the same paper indicates that the body weight is perhaps 13% lower than in the controls during quite a large period of the post-exposure period. Omura, on the other hand, indicates that the body weights of the exposed group is 10-20% lower than of the control group from week 8-64 post exposure. The animals clearly suffer from the pulmonary toxicity of indium phosphide, and it is difficult to assess the health status of the animals, although no systemic signs of general toxicity were observed.

Effects on the male reproductive tract of the hamster are indicated by;

- the sperm count at the end of the exposure period was reduced (by 10%) more than the body weight, and the sperm count was maximally reduced by 60% by week 64,
- the weight of the testis and epididymes being much more reduced (maximally 40%) than the body weight,
- by histopathological changes in the testis (from vacuolization of seminiferous epithelium to atrophy of seminiferous tubules),
- effects being relatively consistent over time during the 88 weeks post-exposure period.

This study provides evidence that indium phosphide induces toxic effects on the male reproductive system. Although some generic toxic effects also occurred, there is no indication that the changes seen in the reproductive system could be secondary to general toxicity. The findings in this study are therefore judged to be relevant for classification.

The non-physiological mode of administration used in this study is not considered to have a significant impact on interpretation of the results compared to inhalation regarding systemic effects such as reproductive effects. It is also notable that the exposure level is very low, and equivalent to a systemic dose of <1 mg/kg/day for the 8 weeks exposure period

By inhalation, effects on the reproductive systems are seen in rats and mice of both sexes, but only at doses inducing very serious toxicity (14-week studies described above). No effects were reported in the 2-year studies in which doses were limited up to 0.3 mg/m3.

Toxicokinetic data show that indium can accumulate in rat testes after inhalation, and accumulation may be assumed in other species, raising a concern for potential accumulation of high concentrations after chronic exposure.

As there is no human information on testicular toxicity available to enable species comparisons, it is prudent to assume that humans could be as sensitive as hamsters.

On the basis of effects on male reproductive organs observed in hamsters and of toxicokinetic data showing an accumulation of indium in testis, the criteria for classification in category 3 for reproductive toxicity (fertility) are met. Similarly, under the criteria of CLP, indium phosphide should be classified in category 2 for reproductive toxicity. It is the view of RAC that hazard statement H361f is the most appropriate, given the available toxicological profile of indium phosphide, but RAC recognised that H361 could be applied if the available criteria are applied strictly.

Classification according to Directive 67/548/EEC: Repr Cat 3; R62

Classification according to the CLP Regulation: Repr 2: H361 (fertility)

5.9 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

Not applicable.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Not evaluated in this dossier

7 ENVIRONMENTAL HAZARD ASSESSMENT

Not evaluated in this dossier

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

The following justification was provided by the submitting French CA on 9th December 2009, following the first discussion in the RAC.

> The substance is carcinogenic and toxic for fertility, effects that justify a harmonised classification and labelling.
>
> This dossier for harmonisation of the classification of Indium Phosphide was initially submitted to the Technical Committee on Classification and Labelling (TC C&L) in 2006, although the dossier has never been discussed by this Committee. In this context, full harmonisation was required and all relevant information was therefore collected. Available data indicate that a classification T; R48/23 for repeated toxicity is justified.
>
> In the absence of the Classification and Labelling Inventory that is not yet available, it is not possible to know what self-classification is applied by manufacturers and importers and if classification for repeated toxicity is adequately applied.
>
> Considering the need for classification for repeated toxicity as shown in this hand-over CLH dossier and the absence of information to confirm its application in industry, action on a community-wide basis is considered to be required to ensure an appropriate and homogeneous application of classification for this endpoint.

The RAC has considered this justification, and although agreeing in principle, RAC has agreed on the following justification.

> In accordance with the REACH and CLP Regulations, the proposals to harmonise classification of indium phosphide for carcinogenic and reproductive effects do not require a special justification for action at Community level.
>
> Indium phosphide is a “transitional substance”, because the dossier was initially prepared under the old legislation (prior to REACH and CLP) with a view to it being considered by the TC C&L expert group. However, that group did not get to discuss it before responsibility for C&L was passed to ECHA. As the data on the high potency lung toxicity was already compiled, a proposal for a harmonised classification of indium phosphide for adverse effects on the lungs after repeated inhalation exposure was included in the submission to ECHA. RAC concluded that this was justified by the need to ensure consistent and helpful labelling for this substance. Application of labelling for repeated dose toxicity will enable information about the key route of exposure of concern to be provided. Provision of this information, about the lungs being a target organ following inhalation exposure, will further help protect against the toxicity/carcinogenicity of indium phosphide.
>
> In relation to repeated dose toxicity, the complexities in deriving a specific concentration limit (SCL) for this endpoint were noted by RAC deliberations, and setting a harmonised SCL therefore also seems of importance for this substance.

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